Impact of compliance to chemoradiation on long-term outcomes in squamous cell carcinoma of the anus. Results of a post-hoc analysis from the randomized phase III ACT II trial

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Running title: Compliance to chemoradiation in the ACTII trial

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ABSTRACT

Purpose: Concurrent chemoradiation is standard-of-care for patients with squamous cell carcinoma of the anus (SCCA). Poor compliance to chemotherapy, radiotherapy treatment interruptions and unplanned breaks may impact adversely on long-term outcomes.

Methods: The ACT II trial recruited 940 patients with localized SCCA, and assigned patients to mitomycin (week 1) or cisplatin (weeks 1 and 5), with fluorouracil (weeks 1 & 5) and radiotherapy (50·4 Gy in 28 fractions over 38 days). This post-hoc analysis examined the association between baseline factors (age, gender, site, T-stage and N-stage), and compliance to treatment (radiotherapy and chemotherapy), and their effects on loco-regional failure-free survival (LRFFS), progression-free survival (PFS) and overall survival (OS).

Compliance was categorized into groups. Radiotherapy: 6 groups according to total dose (TD) and overall treatment time (OTT): Chemotherapy 3 groups: (A = per-protocol; B = dose reduction or delay; C = omitted).

Results: 931/940 patients were evaluable for radiotherapy and 936 for chemotherapy compliance. Baseline Glomerular filtration rate (GR) <60 mL/min and cisplatin were significantly associated with poor week 5 compliance to chemotherapy (p 0.003 and 0.02, respectively). Omission of week 5 chemotherapy was associated with significantly worse LRFFS (HR 2.53 [1.33 to 4.82] p=0.005). Dose reductions/delays or omission of week 5 chemotherapy were associated with significantly worse FPFS

(HR: 1.56 [95%CI: 1.18-2.06], p=0.002 and HR: 2.39 [95%CI: 1.44-3.98}, p=0.001, respectively) and OS (HR: 1.92 [95%CI: 1.41-2.63], p<0.001 and (HR: 2.88 [95%CI: 1.63-5.08], p<0.001, respectively). Receiving the target radiotherapy dose in >42 days is associated with worse PFS and OS (HR:1.72 (95%CI:1.17-2.54), p=0.006).

Conclusion: Poor compliance to chemotherapy and radiotherapy were associated with worse LRFFS, PFS and OS. Treatment interruptions should be minimized, and OTT and TD maintained**.**

277 words

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Introduction

Standard treatment for localized squamous cell carcinoma of the anus (SCCA) is chemoradiation using concurrent fluorouracil and mitomycin C[1,2] This combination has been tested in randomized trials[3,4,5,6,7] and results in good outcomes for cT1/T2 cancers[7], but less so for cT3/T4 cancers[7,8]**.** Loco-regional failure is the predominant pattern of relapse[7,9], potentially influenced by innate chemo/radio-resistance, sub-therapeutic radiotherapy total dose (TD) delivered and poor chemotherapy compliance.

Early phase III trials in SCCA planned breaks in treatment of 6-8 weeks to manage acute treatment-related toxicities[3,4,] Evidence for the importance of overall treatment time (OTT) exists in squamous carcinomas of the head and neck (SCCHN)[10,11]. Evidence in SCCA is inconsistent, but strict adherence to protocol achieved significantly better overall survival (OS)[12] and suboptimal compliance to the planned radiotherapy TD adversely impacted on local control and OS[13]. More recent trials, without planned radiotherapy interruptions, reported high levels of acute toxicity to both modalities[6,7]**,** leading to poor compliance in some patients. With the increasing use of intensity modulated radiotherapy (IMRT), toxicity is reduced allowing a potential reduction in average OTT[14].

Since chemotherapy and radiotherapy independently enhances the other, compliance for each is required for optimum results. In the second United Kingdom Anal Cancer Trial (ACT II) the intention was to deliver a standard central axis tumour dose (irrespective of stage) of 50.4Gy in 28 fractions in 38 days. Other contemporary trials

used an initial dose of 45Gy, but were permissive, according to stage and response, as regards TD and number of fractions[6,15].

Compliance refers to conformity to trial recommendations with respect to timing, dose, and frequency of the intended radiotherapy or chemotherapy treatment. We could find no standard definition for radiotherapy compliance (TD or OTT) within chemoradiation schedules in SCCA, although the UK contemporary national guidance in 2015 recommended a maximum of 4 days extension to the OTT[16]**.** In contrast, the RTOG 9811 trial allowed treatment breaks up to 10 days[6]. Thus ACT II, is uniquely placed to reliably assess the impact of compliance in terms of TD, OTT and chemotherapy on cancer outcomes. The permissive design of the other randomised trials precludes such an analysis.

The present analysis aimed to quantify compliance to radiotherapy (TD and OTT) and week 5 chemotherapy. We aimed to identify independent factors to predict better or worse compliance, and to investigate the impact on oncological outcomes i.e. loco-regional failure-free survival (LRFFS), progression-free survival (PFS) and OS). This is a relevant research question, which cannot be answered by only looking at those patients with poorer compliance.

Materials and Methods

Trial design and participants

ACT II was a randomized factorial phase III trial with 940 patients enrolled between 2001-2008, which investigated whether replacing mitomycin with cisplatin in the chemoradiation schedule improves complete response rate, and the impact of maintenance chemotherapy (fluorouracil/cisplatin) after chemoradiation. Methods and results have previously been reported[7].

Protocol Guidance and modifications for toxicity

Radiotherapy: All patients were to receive radiotherapy (50.4Gy in 28 daily fractions over 38 days), in two-phases to the International Commission on Radiation Units and Measurements (ICRU) intersection point. A Monday start for radiotherapy was recommended, but not mandated. As such, planned OTT for those commencing treatment Monday to Wednesday or Thursday to Friday would be 38 and 40 days respectively. Protocol interruptions to radiotherapy were only recommended for haematological and gastrointestinal NCI Common Toxicity Criteria (CTC) grade 3 and 4. The protocol did not encourage, but allowed clinician's discretion to interrupt radiotherapy for moist skin desquamation, gastrointestinal and haematological toxicity. There was no guidance in the protocol about how, or when, to compensate for such interruptions.

Chemotherapy: Patients received fluorouracil 1000 mg/m² per day on days 1–4 (week 1) and 29–32 (week 5) by continuous intravenous infusion with radiotherapy, and either, 12 mg/m² of mitomycin as an intravenous bolus on day 1 only (maximum single dose 20 mg), or 60 mg/m² of cisplatin by intravenous infusion on days 1 and 29 (maximum single dose of 120 mg).

Patients with a calculated GFR of 50-60 ml/min were eligible only if the subsequently tested GFR was ≥ 50ml/min. Cisplatin and MMC dose reductions were prescribed for patients with a GFR of 50–59 mL/.

Fluorouracil doses were reduced for week 5 chemotherapy in severe toxicity following week 1. Specifically, 25% and 50% dose reductions were recommended for grade 3 and 4 haematological toxicity respectively. Omission of fluorouracil was mandated in the case of G4 diarrhoea. Week 5 cisplatin was omitted if the GFR fell below 50ml/min.

Radiotherapy interruptions for toxicity delayed chemotherapy, so that the two modalities were given together.

Treatment compliance definition

Per-protocol radiotherapy compliance was defined prior to analysis as completion of protocol radiotherapy 50.4 Gy in 28 fractions within an OTT of 38-42 days (including up to 4 days for logistical problems and public holidays) i.e. 10% extension. Poor radiotherapy compliance was therefore defined as extending >42 days. **Table 1** shows how we categorized radiotherapy and week 5 chemotherapy compliance.

Statistical analysis

Categorical variables were summarized in terms of frequency and percentage, and continuous variables in terms of median and range.

The association between baseline factors and radiotherapy TD delivered was examined using Kruskall Wallis test. The OTT by groups 1-6 was evaluated using cox regression. Logistic regression assessed any association between baseline characteristics and the risk of radiotherapy interruptions due to toxicity and odds ratios

(OR), 95% CI and p-values are reported. Fisher's exact test examined whether any baseline characteristics were associated with chemotherapy compliance.

Kaplan-Meier plots and cox regression assessed the effect of radiotherapy/chemotherapy compliance (groups 1-6 and A-C) on PFS and OS with subgroup analysis by T-stage. To account for potential immortality bias, the time to event outcomes were measured as time from 7 weeks post registration until the event of interest, or date of last follow-up for censored patients. Hazard ratios (HR), 95%CI and p-values derived from cox regression are reported.

RESULTS

Radiotherapy

Of 940 patients, 931 were evaluable for radiotherapy and 936 for chemotherapy compliance respectively **[Figure 1].** Median follow-up was 5.1 years (95%CI: 5.0-5.3). **Table 2,** shows baseline characteristics were similar amongst all patients, and amongst groups 1-6 and groups A-C, except week 5 chemotherapy delays and reductions were more common in the cisplatin arm and amongst patients with GFR≥60 mL/min.

Previously reported compliance details[7] have been updated. **[Table 3].** The median radiotherapy TD was 50·4 Gy (range 5.6Gy – 56.7Gy, IQR 50·4–50·4) in a median of 28 fractions (range 3-32). Median OTT for radiotherapy was 38 days (range 3-81 days, IQR 38–39). 98/931 (11%) patients had at least one day's interruption in radiotherapy documented due to toxicity, but the precise cause was not specified in 82/98 patients (84%). A further 40/931 (4%) had interruptions due to non-toxicity (19 administrative

i.e. machine breakdown, transport) 11 patient choice (weather, illness) and in 10 the reason was not specified. Only 18 patients had treatment interruptions of ≥8 days. For the 15 patients in Group 6, the extension to OTT ranged from1-29 days with a median of 7 days. Radiotherapy was completed as per-protocol in 379/467 (81%) in the mitomycin arm and 377/464 (81%) in the cisplatin arm respectively. There was no evidence of an association between baseline factors, type of chemotherapy (mitomycin, cisplatin), age, gender, clinical T or N stage, GFR, WBC and radiotherapy compliance **[Table A1 & A2]**.

Adjusting for interruptions due to toxicity, we observed a statistically significant effect of radiotherapy OTT on PFS and OS - if patients receive less than the planned target dose or if the planned target dose is extended >42 days **[Figure 2 and Online Table A3, Figure A1, Figure A2].** Patients who received the planned radiotherapy dose within 38-42 days had better outcomes. If OTT was extended >42 days, there was a significant increase in the risk of PFS event and death (PFS, HR: 1.58 (95%CI: 1.12 to 2.23) p=0.01) (OS, HR: 1.72 (95%CI: 1.17 to 2.54), p=0.006).

Chemotherapy

Week 1 chemotherapy was delivered without reductions/delays to 99% of patients in both mitomycin (433/465) and cisplatin arms (429/464). Chemotherapy delays or per-protocol reductions were uncommon; 32/465 (7%) in the mitomycin and 33/464 (7%) cisplatin arm

Data on week 5 chemotherapy was available for 936 patients. No chemotherapy was administered to 35/936 (3.7%), and 14% (68/471) in the mitomycin and 21% (96/465) in the cisplatin arm had delays or reductions. Completion of week 5 chemotherapy per-protocol was higher in the mitomycin arm 388/471 (82%) compared to the cisplatin arm 349/465 (75%). Poor compliance reflected acute toxicity, mainly haematological toxicity, worsening renal function, mucositis, diarrhoea and severe asthenia.

There was no association between baseline factors and week 5 chemotherapy compliance, except for baseline GFR in mL/min (p=0.003) (**Table A2**). Patients with baseline GFR of ≥60mL/min were more likely to receive week 5 per-protocol chemotherapy, 711/891 (80%) compared with <60mL/min - 26/45 (58%).
The week 5 chemotherapy 5FU intensity is comparable in both the mitomycin and cisplatin arms.

Dose reductions/delays or omission of week 5 chemotherapy were associated with worse LRFFS (HR:1.35 [0.92 to 1.98] p=0.13 and HR 2.53 [1.33 to 4.82] p=0.005 respectively). There was a statistically significant association between receiving per-protocol week 5 chemotherapy and PFS (p=0.0006) and OS (p<0.0001) **[Figure 3, Table A4]**. Omission of chemotherapy during chemoradiation was associated with >2-fold increase in the risk of a PFS event (HR: 2.39 (95%CI: 1.44 to 3.98), p=0.001) compared with patients who completed week 5 per-protocol and an increased risk of death (HR 2.88 (95%CI: 1.63 to 5.08), p<0.001). Patients who received week 5 chemotherapy with delays/reductions compared with per-protocol, also had a significant increased risk of a PFS event (HR: 1.56 (95%CI: 1.18 to 2.06), p=0.002) and death (HR: 1.92 (95%CI: 1.41 to 2.63), p<0.001).

There is evidence of an interaction between chemotherapy week 5 compliance and T-stage for PFS (p=0.04) and OS (p=0.04) (**Table A4 and Fig 3**). The findings suggest patients with more advanced T-stage (T3-4) who failed to receive per-protocol week 5 chemotherapy have a worse PFS (p<0001) and an increased risk of death (p<0001) compared with per-protocol treatment (**Table A5**).

Compliance varied within the 52 participating sites, particularly in the 16 (31%) which recruited <10 patients **(Figure A3).** The impact of facility volumes and academic centres on outcomes has been highlighted in SCCHN [17]. In ACT II, these 16 hospitals treated 79 patients; 30 of whom (38%) did not complete per-protocol treatment, compared with 36 sites entering ≥10 patients where only 145/852 (17%) did not complete per-protocol treatment. Amongst sites recruiting ≥10 patients, the correlation between the number of patients recruited in each site and the percentage of patients who received radiotherapy as per-protocol was weak and not statistically significant (Spearman correlation coefficient=-0.20, p value = 0.24).

Discussion

ACT II mandated a TD (irrespective of stage) of 50.4Gy in 28 fractions in 38 days. This retrospective post-hoc analysis quantifies compliance of patients treated with chemoradiation in the trial. We demonstrated that extending OTT of radiation by >42 days, and the omission of week 5 chemotherapy or reduced doses/delays are associated with inferior PFS and OS. This represents important information for clinicians treating this rare disease.

Since the protocol mandates chemotherapy and radiation are delivered concomitantly, 40% of patients who had a delay of radiotherapy OTT >42 days, also had the week 5 chemotherapy delayed and/or dose reduced, but only 4% had no chemotherapy at all. The association between better chemotherapy week 5 compliance in the patients who had RT as per protocol compared with patients who had RT prolonged with OTT >42 days (40.4% vs 13.76% [p<0.001] respectively implies that the inability to deliver the radiotherapy in a timely fashion is the main driver of the poor outcomes.

A retrospective pooled analysis of the RTOG 87-04 and RTOG 98-11 trials (Ben Josef 2010) concluded that total treatment time, but not duration of radiation therapy, has a detrimental effect on local failure and colostomy rate in anal cancer. However, a third received NACT and 62% of patients in RTOG 9811 required a treatment break resulting in an overall median OTT of 49 days and 302/644 (47%) patients received a total dose of only 45Gy. For these reasons, the data cannot be compared with our data in ACT II, which gave no NACT, used a mandated dose of 50.4Gy, and treatment breaks for skin toxicity were not permitted.

The strength of the study is that the data was collected prospectively within the ACT II trial with a large number of patients in study arms with equal distribution of age, gender, clinical stage of disease, ECOG performance status, and localization of primary tumour (canal /margin). TD, the fraction size of radiation and hence biological equivalent dose (BED) and the chemotherapy protocols were highly homogeneous. In particular the consistency of the OTT [median 38 days (IQR 38-39 days)] in both mitomycin and cisplatin groups strengthens our conclusions. Outcomes are also mature with a 5-year median follow-up.

Quality assurance (QA) in radiotherapy has previously focussed on target delineation, dosimetry, PTV coverage or dose-volume parameters, OTT has been less rigorously assessed. Compliance has been categorized as acceptable, unacceptable and other (no radiotherapy or incomplete radiotherapy due to death, progression or refusal)[18]. Some trials consider a tolerance of +/- 10% as per-protocol with >10% an unacceptable deviation[19]. In ACT II, the QA protocol did not specify how many days extension to OTT would classify minor or major deviations.

The limitations of this study include the fact that this was an unplanned 'post hoc' retrospective analysis. The groups were retrospectively defined (based on contemporary UK recommendations and +/- 10% deviations), but the definitions were set prior to any analysis of data. Since patients are not randomized into these groups, sources of bias cannot be controlled for. Few patients failed to achieve per-protocol compliance and hence these represent small subgroup analyses.

Larger field sizes could have contributed to toxicity and compliance, but without reviewing individual field sizes in the light of staging CT and MRI scans to assess their fidelity, we are unable to provide detailed data. However, it is reassuring that median radiotherapy TD delivered, OTT for radiotherapy and risk of radiotherapy interruptions due to toxicity are similar between T1, T2, T3 and T4 tumours, and there is no evidence of a statistical difference (p= 0.68, p=0.47 and p=0.88 respectively). **Table A1.** Reductions/delays in week 5 chemotherapy was observed in 15% for T1/T2 and 19% for T3/T4, with no statistically significant difference (p=0.37) **Table A2.**

A further limitation is that we were unable to test for imbalances between the groups in human papilloma virus–associated cancer (p16+), smoking history or tumour infiltrating lymphocytes as this data was not collected and we were unable to adjust for co-morbidity.

The association between compliance groups and outcomes can reflect an outcome-by-outcome analysis, which is prone to bias as patients who complete per-protocol treatment tend to be younger, fitter, more robust, without co-morbidity and hence have a better prognosis. Any association between compliance and outcome does not therefore necessarily mean that the actual treatment received is associated with better/worse outcomes, although if other reasons such as poor adherence without toxicity and administrative issues can be shown to be responsible, then more robust associations can be drawn. Our results show no difference in the proportion of patients with an OTT >42 days for patients $\geq$ 65 years compared to younger patients.

There are a number of potential strategies to improve compliance. Prospective data from the RTOG 0529 trial suggest IMRT reduces acute toxicity. Significant reductions were reported in grade 2+ hematologic (73% vs. 85%; P= .032), grade 3+ gastrointestinal (21% vs. 36%; P = 0.008), and grade 3+ dermatologic events (23% vs. 49%; P<0.0001)[14]. Subsequent analyses suggested acute AEs correlated with radiation dose to the small bowel and anterior pelvic contents[20] in keeping with the finding of improved toxicity using IMRT. This is similar to a UK audit of SCCA, where reduced toxicity resulted in radiotherapy interruptions falling from 8%-4% with IMRT and patients completing planned radiotherapy TD rose from 90% to 96%[21].

Despite the use of IMRT, compliance remains an issue since treatment breaks in the 51 assessable patients in the RTOG 0529 trial were required by 49%, compared with 62% in RTOG 9811 (P=0.09), Median OTT with IMRT was 43 days with TD 54Gy, compared with 49 days and TD 50.4Gy in the standard fluorouracil/mitomycin arm of RTOG 9811l (P<0.0001)[14]. Additionally, 8/51 (16%) patients did not complete per-protocol chemotherapy. A recent retrospective pooled analysis of patients treated with IMRT in the UK reported failure to complete treatment or interruptions (defined as any extension >2 days over the planned OTT) as 5.2%. In multivariate analysis a HR of 5.80 (1.96-17.29) was found in this group for persistent disease (p=0.001) compared with treatment delivered per-protocol[22]. Therefore, despite IMRT, poor compliance remains an issue.

A retrospective analysis, using the National Cancer Data Base (NCDB), compared outcomes of patients with SCCA treated with IMRT or 3D-CRT[23]. They reported improved OS for those treated with shorter treatment times (P < .0001) and at high-volume centers [>18 cases per-year] (P = .0011). A more recent NCDB analysis of CRT (2004–2014), also showed prolonging RT was independently associated with reduced OS - with most effect when RT was delayed $\geq$2 days[24].

Additional proactive strategies could further improve compliance. First, meticulous hydration in the first cycle of chemotherapy might minimize toxicity in patients with baseline GFR<60. Second, the association between absolute nadir and the V10/V20 of pelvic and lumbosacral bone marrow could be addressed by bone marrow sparing, optimising constraints and plan evaluation[24].

Data on chemotherapy compliance in SCCA is sparse **(Table A6).** In the ACCORD 03 trial 78/82 (95%) (Arm C) and 71/75 (95%) (Arm D) received the second cycle of concurrent chemotherapy in the 157 patients, who received chemoradiation without induction chemotherapy[15]. However, this second cycle was adjusted (50-75%) according to early toxicity.

In ACT II prolonged OTT in radiotherapy and poor compliance to week 5 chemotherapy were associated with worse PFS and OS outcomes. The large randomised trial dataset with standardised radiotherapy fields and the same mandated total dose, protocol-defined chemotherapy and toxicity prospectively captured, increases the likelihood that our findings are applicable to routine clinical practice, and should have a significant impact on the delivery of treatment regimens.

Although a 'post hoc' analysis is not powered for comparisons, the data can assist the design of future trials. We believe that there is an unmet need for studies to identify factors associated with compliance, and whether compliance could be used as a `marker' predictive of the outcome. In this study, prolongation of OTT was not associated with any clinical factors, but initial GFR impacted on the ability to deliver week 5 chemotherapy in full.

This analysis strongly suggests radiotherapy should be delivered per-protocol in a timely manner in high volume facilities, avoiding interruptions, to achieve optimal treatment outcomes. Better outcomes are observed when week 5 chemotherapy is administered in full without dose reduction or delay. Patients with poor compliance

may require closer monitoring following chemoradiation to identify local recurrence at an early stage.

Contributors

RGJ, AL & HM designed this post hoc study, AL did the statistical analysis, RGJ, AL & HM wrote the paper, all authors interpreted the data and reviewed and approved the final draft.

Declaration of Interest

We declare no competing interests.

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